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Synthesis of iboga alkaloids by Pd-catalyzed heteroannulation of 2-iodoaniline with an internal alkyne as the key step

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ABSTRACT

A convenient synthetic route to the iboga-scaffolds is described. Important steps include a Pd-catalyzed regiospecific indole formation between internal alkyne-substituted isoquinuclidine and 2-iodoaniline. The final cyclization was done using Trost's Pd(II)–Ag(I) mixed-metal-mediated cyclization method originally developed for the synthesis of ibogamine. Both *exo*- (iboga) and *endo*-isomers (epi-iboga) at C-19 substitution with $-CO_2Me$ have been reported.

Iboga alkaloids comprise a large group of pharmacologically important indole alkaloids, isolated from the root bark of the African shrub *Tabernanthe Iboga*. Members of this family of alkaloids have characteristic indole and isoquinuclidine ring fused by a seven-membered indoloazepine ring[1] (Fig. 1). A total of 19 iboga-like alkaloids have been reported[2] in which seven have been isolated recently. These natural products have attracted attention because of their reported ability to reverse human addiction to multiple drugs of abuse, including alcohol, heroin, cocaine.[3] Apart from anti-addictive properties, iboga alkaloid congeners show potent leishmanicide effects against *Leishmania amazonensis*.[4] Although these alkaloids show important biological activities, natural ibogaine **2** causes several side effects such as hallucinations, degeneration of cerebeller purkinje cells,[5] whole body tremors and ataxia in rats[6] if the dose is high. Since chemical modifications of the natural product have been the major means for exploration of the more potent analogues, a limited number of its analogues have so far been accessible.[7] Thus an efficient synthetic route is necessary for the synthesis of iboga alkaloids and their analogues around the iboga scaffold that might be useful for the evaluation of pharmacological profiles and their biological (receptorial) target.[8] Büchi et al. were the first to disclose a successful synthesis of racemic ibogaine and ibogamine as well as the corresponding unnatural C(20)-epimers[9] and several other syntheses followed.[10] Mostly, the reported syntheses began with β-indolyl acetyl chloride, tryptophyl bromide or tryptamine as starting material.

However, these methods require a prefunctionalized heterocyclic indole for the modification of indole sub-system of iboga alkaloids in order to have heterocyclic analogues **5**. But a limited number of prefunctionalized heterocyclic indoles are commercially available and are very expensive. In addition, the reported syntheses (except for a few[7a,c]) lack the flexibility required to provide access to the more elaborate representatives on both indoloazepine and isoquinuclidine rings **5**.

Herein we describe a convenient approach to the synthesis of iboga **6a** and epi-iboga **6b** scaffolds (Scheme 1) using Larock heteroannulation reaction[11] as the key step. As can be seen from our retrosynthetic analysis of iboga-system **6** if the C2-C16 bond is disconnected, the new target molecule will be 2,3-disubstituted indole, **7** (when R = $SiMe_3$) or 3-substituted indole, **8** (when R = H).

Further strategic disconnection of compound **7** shows the presence of 2-iodoaniline and alkyne-substituted isoquinuclidine **9**. Synthesis of the requisite isoquinuclidine-substituted internal alkyne **9** for the palladium-catalyzed 2,3-disubstituted indole formation is outlined in Scheme 2. The isoquinuclidine ring **9** was synthesized by heating the mixture of Cbz-protected dihydropyridine[12] and methyl acrylate at 160 °C for 40 h in a sealed tube and this was slightly different from the procedure reported by Büchi et al.[9] Moreover, a single regioisomer **10** was obtained as pyridine was used as a starting material instead of 3-substituted pyridine. The separation of the *exo*- and *endo*-isomers was difficult at this stage though its separation was reported[13] earlier via the formation of iodolactone in a multistep process. Here we used the material **10** directly in the next step.

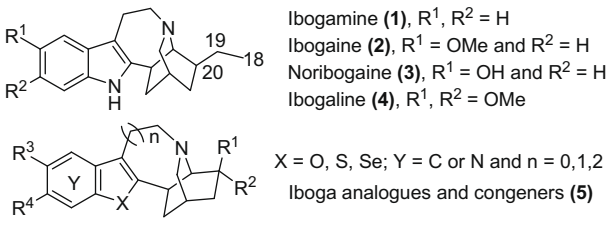

Figure 1. Iboga alkaloid family.

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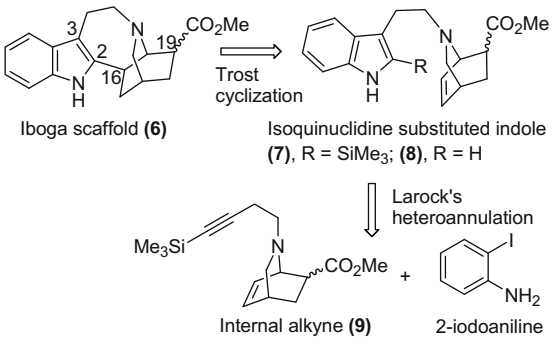
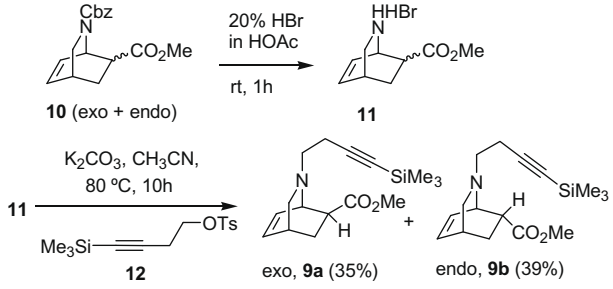


Scheme 1. Retrosynthetic strategy.



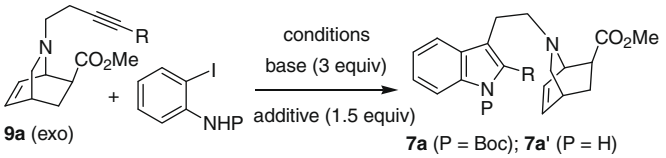
Scheme 2. Synthesis of isoquinuclidine substituted alkynes.

After Cbz-deprotection with 20% HBr/HOAc, the compound **11** was converted to the alkynylated isoquinuclidine **9** and its mixture of *exo*- and *endo*-isomers was then separated by column chromatography on silica gel to give **9a** and **9b**, respectively, in a 1:1.1 ratio (Scheme 2). These were characterized by ^{1}H NMR. The tosylated alkyne was in turn synthesized from 3-butyn-1-ol, which was then converted to the silylated compound **12** in the presence of *n*-BuLi with trimethylsilyl chloride. The overall yield was 70% in two steps. We next investigated the construction of 2,3-disubstituted indole **7** via Larock heteroannulation reaction (Table 1). Initial attempts at the heteroannulation reaction of 2-iodoaniline with internal alkyne **9a** under Larock's condition[11] in the presence of LiCl (1.5 equiv) gave a complex mixture (entries 1 and 2). The reaction gave 24% isolated yield when *n*-Bu_4NCl (1.5 equiv) was used instead of LiCl (entry 3) and the yield was improved to 36% in the presence of 10% PPh_3 as a ligand (entry 4). Further screening with Boc-protected-2-iodoaniline and PPh_3 as a ligand was performed and both K_2CO_3 and Na_2CO_3 gave moderate yields (entries 5 and 6). We were pleased to find that diisopropylethylamine (DIPEA) improved the yield to 73% even at low temperature (entry 7). Unprotected 2-iodoaniline again gave a moderate yield even when the same base was used (entry 8).

These observations reveal that protecting group as well as base and additives influenced this Pd-catalyzed reaction. The isoquinuclidine bearing 2,3-disubstituted indole **7a**, a Trost ibogamine-like precursor (indole NH was unprotected), was then cyclized using the Trost mixed-metal-mediated cyclization method[10f] developed for the synthesis of ibogamine. After Boc-deprotection, iboga scaffold **6a** was obtained in 31% yield (Scheme 3).

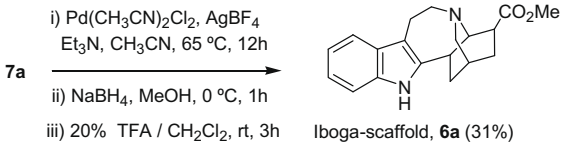
The optimized condition of 2,3-disubstituted indole **7a** formation (entry 7, Table 1) was then applied to the coupling of Boc-protected 2-iodoaniline with *endo*-isomer **9b**, but disappointingly the reaction gave a complex mixture with very low consumption of 2-iodoaniline. This is perhaps due to the unfavorable steric and electronic factors in the transition state by the *endo*-CO_2Me group at

Table 1
Synthesis of 2,3-di-substituted indole **7a**[a]



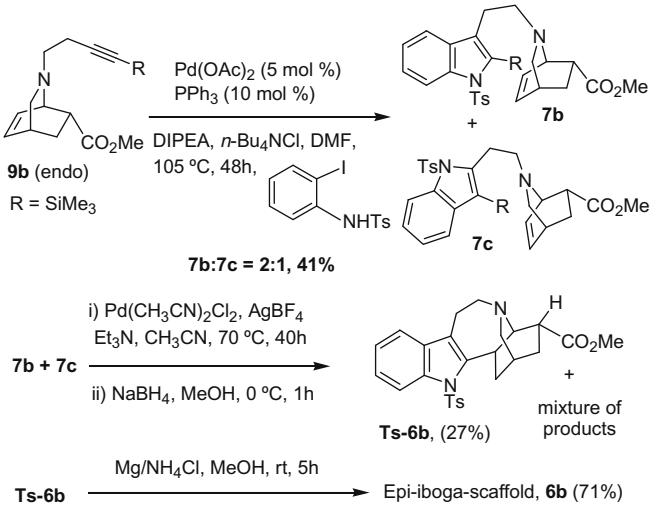
Entry	P	Pd/Ligand	Base	Time (h)	Temp (°C)	Yield[b] (%)
1[c]	H	$Pd(OAc)_2$	K_2CO_3	16	100	Trace[e]
2[c]	H	$Pd(OAc)_2$	Na_2CO_3	20	100	Trace[e]
3[d]	H	$Pd(OAc)_2$	K_2CO_3	16	100	24
4[d]	H	$Pd(OAc)_2/PPh_3$	K_2CO_3	15	100	36
5[d]	Boc	$Pd(OAc)_2/PPh_3$	K_2CO_3	15	100	46
6[d]	Boc	$Pd(OAc)_2/PPh_3$	Na_2CO_3	15	100	35
7[d]	Boc	$Pd(OAc)_2/PPh_3$	DIPEA	10	75	73
8[d]	H	$Pd(OAc)_2/PPh_3$	DIPEA	12	80	41

[a] Reactions were carried out in DMF using alkyne **9a** 1.2 equiv Pd (5 mol %)/ligand (10 mol %).
[b] Isolated yields.
[c] Additive LiCl.
[d] Additive *n*-Bu_4NCl.
[e] Yields not determined.



Scheme 3. Synthesis of iboga scaffold **6a**.

the C-19 position. We have tried several other conditions such as using a different catalyst [$Pd(dppf)_2Cl_2$], and an excess amount of alkyne **9b** (up to 2.5 equiv) but in all these cases the yield was very poor and it was difficult to purify the product. Then we changed the protecting group and found that tosyl-protected 2-iodoaniline gave the coupling products **7b** and **7c** (regioisomer) as an inseparable mixture in 41% yield. The ratio **7b**:**7c** (2:1) was determined based on the integration value of ($SiMe_3$) by ^{1}H NMR. The mixture was then cyclized under Trost's conditions to give tosylated **6b** in 27% yield and an inseparable mixture of desilylated starting material and other products. The removal of the tosyl group of **Ts-6b** by using Mg metal/NH_4Cl in methanol[14] at rt afforded epi-iboga scaffold **6b** with CO_2Me substitution at C-19 in 71% yield (Scheme 4).



Scheme 4. Synthesis of epi-iboga scaffold **6b**.

In summary, we have developed a new approach toward the synthesis of iboga alkaloids using palladium-mediated coupling reactions as the key steps. Our synthetic approach is extremely short and flexible and we obtained *exo*-product **6a**[15] in high yield (overall yield 21% from 2-iodoindole) that belongs to the natural product skeleton and its analogue **6b** (*endo*-product, called epi-iboga) as well. It is anticipated that minor modifications of the starting materials and methods presented here should provide access to related members and analogues of this alkaloid family **5** (Fig. 1) and could be useful for the total synthesis of some newly isolated iboga alkaloids.[2b] Work toward such ends is now underway and results will be reported in due course.

Acknowledgments

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15. *Experimental section and spectral data for some key compounds*: Compounds **9a** and **9b**. An oil containing mixture of *exo*- and *endo*-isomers **10** (2.20 g, 7.30 mmol) was dissolved in 20% hydrogen bromide/acetic acid (15 mL) and stirred for 1 h. The solution was evaporated in vacuo to dryness to give a mixture of hydrobromide salt **11** (*exo* + *endo*) (1.81 g, 100%) which was directly used in the next step. A suspension of K_2CO_3 (2.0 g, 14.60 mmol) in anhyd CH_3CN (12 mL) containing the above-mentioned deprotected isoquinuclidine **11** (1.81 g, 7.30 mmol) and alkyne **12** (2.16 g, 7.30 mmol) was refluxed for 10 h then cooled to room temperature and filtered through a pad of Celite and washed with EtOAc (10 mL). The combined organic extracts were concentrated in vacuo and purified by column chromatography on silica gel (3–10% EtOAc in petroleum ether) to give isoquinuclidine containing alkyne **9a** (734 mg, 34.5%), (R_F = 0.48, PE/EtOAc, 9:1) and **9b** (820 mg, 38.6%) as a colorless oil (R_F = 0.42, PE/EtOAc, 4:1).
Exo **9a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (t, J = 7.26 Hz, 1H), 6.21 (dd, J = 7.29, 6 Hz, 1H), 3.78 (m, 1H), 3.70 (s, 3H), 3.11–3.07 (dd, J = 9, 2.1 Hz, 1H), 2.65–2.58 (m, 1H), 2.51 (br m, 1H), 2.42–2.36 (dt, J = 11, 3.4 Hz, 1H), 2.4–2.31 (m, 2H), 2.20 (m, 1H), 2.15–2.08 (dt, J = 14.7, 2.9 Hz, 1H), 1.85–1.82 (dt, J = 9, 2.3 Hz, 1H), 1.39–1.31 (ddt, J = 12.7, 9.5, 2.8 Hz, 1H), 0.116 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 135.3, 129.9, 105.9, 84.9, 56.8, 54.8, 54.7, 51.9, 45.4, 31.0, 24.3, 19.9, 0.23; IR (neat): ν 3045, 2948, 2172, 1738, 1250 cm^{-1}; HRMS (ESI): $(M+H)^+$ calcd for $C_{16}H_{25}NO_2SiH^+$ 292.1727; found 292.1728.
Endo **9b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (t, J = 7.0 Hz, 1H), 6.15 (ddd, J = 6.8, 5.5, 1 Hz, 1H), 3.79 (ddd, J = 6, 3.3, 1.1 Hz, 1H), 3.61 (s, 3H), 3.08–3.02 (m, 1H), 2.92–2.88 (dd, J = 9.4, 2.0 Hz, 1H), 2.73–2.68 (m, 1H), 2.56 (br. m, 1H), 2.46–2.40 (m, 1H), 2.35–2.29 (m, 2H), 2.0–1.96 (dt, J = 9.4, 2.3 Hz, 1H), 1.70 (m, 2H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 134.7, 129.7, 105.6, 85.2, 56.9, 54.5, 54.2, 51.8, 43.9, 30.7, 26.0, 20.0, 0.19; IR (neat): ν 3047, 2953, 2174, 1739, 1435 cm^{-1}; HRMS (ESI): $(M+H)^+$ calcd for $C_{16}H_{25}NO_2SiH^+$ 292.1727; found 292.1721.
Compound **7a**. A dry flask was charged with *N*-Boc-2-iodoaniline (356 mg, 1.11 mmol), isoquinuclidine containing internal alkyne **9a** (389 mg, 1.33 mmol), palladium(II) acetate (12.5 mg, 0.055 mmol), triphenylphosphine (29.2 mg, 0.11 mmol), *n*-tetrabutylammonium chloride (463 mg, 1.67 mmol), diisopropylethylamine (0.75 mL, 4.46 mmol) and DMF (8 mL) under an argon atmosphere and heated at 75 °C for 10 h. The reaction mixture was cooled to room temperature and DMF (volatile materials) were removed under reduced pressure. Then ethyl acetate (5 mL) and water (5 mL) were added to the residue. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with 5% $NaHCO_3$ (10 mL) and brine (10 mL) and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (19:1 PE/EtOAc). The *exo*-product **7a** was obtained as a light brown sticky material (392 mg, 73%). R_F = 0.49 (PE/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 8.2 Hz, 1H), 7.53 (dd, J = 7.5, 1 Hz, 1H), 7.32–7.20 (m, 2H), 6.49 (dd, J = 7.35, 7.0 Hz, 1H), 6.26 (dd, J = 6.6, 5.6 Hz, 1H), 3.93 (m, 1H), 3.79 (s, 3H), 3.30–3.27 (dd, J = 9, 2.1 Hz, 1H), 3.05–2.95 (td, J = 13, 5 Hz, 1H), 2.90–2.80 (td, J = 12.5, 5 Hz 1H), 2.65–2.55 (m, 2H), 2.52–2.46 (dt, J = 11, 3.6 Hz, 1H), 2.42–2.33 (m, 1H), 2.28–2.21 (dt, J = 12.7, 2.9 Hz, 1H), 1.99–1.96 (dt, J = 9, 2.2 Hz, 1H), 1.72 (s, 9H), 1.50–1.39 (ddt, J = 12.8, 9.5, 2.6 Hz, 1H), 0.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 151.5, 137.1, 136.4, 135.2, 131.9, 130.6, 129.7, 124.6, 122.1, 118.8, 115.3, 83.5, 59.6, 55.22, 55.0, 51.9, 45.5, 31.1, 28.3, 24.9, 24.3, 2.36; IR (Neat): ν 3045, 2976, 2947, 1726, 1585, 1552, 1448 cm^{-1}; HRMS (ESI): $(M+H)^+$ calcd for $C_{27}H_{38}N_2O_4SiH^+$ 483.2674; found 483.2670.
Compound **6a**. To a slurry of bis(acetonitrile)palladium dichloride (179 mg, 0.70 mmol) in CH_3CN (1.5 mL) was added Et_3N (46 μL, 0.35 mmol) under an argon atmosphere. Silver tetrafluoroborate (275 mg, 1.40 mmol) was added and the orange heterogeneous mixture immediately became yellow. After 10 min, a solution of dehydroisoquinuclidine **7a** (150 mg, 0.35 mmol) in CH_3CN (2.0 mL) was added. The deep red solution was then stirred for 1 h at room temperature then heated at 65 °C for 12 h. The reaction mixture was cooled to 0 °C, MeOH (1.5 mL) was added, followed by $NaBH_4$ (13 mg, 0.35 mmol) in portions. The solution was stirred for 1 h at 0 °C, water (1 mL) was added and the solution was acidified with cold 2 N aq HCl. The mixture was filtered through a pad of Celite to remove palladium black, extracted with ether (20 mL) then basified with cold concd aq NH_4OH. The basic aq solution was extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried, concentrated in vacuo to give *N*-Boc protected and deprotected crude mixture which was used without purification in the next step.
The crude mixture was treated with 20% TFA in CH_2Cl_2 (2 mL) at 0 °C and then the reaction mixture was stirred for 3 h at room temperature. CH_2Cl_2 and volatiles were removed in vacuo and then saturated aq $NaHCO_3$ solution (3 mL) and ethyl acetate (5 mL) were added to the residue. The aqueous phase was extracted with ethyl acetate (3 × 10 mL); the combined organic extracts were washed with brine (10 mL) and the solvent was removed by rotary evaporation. The crude product was purified by silica gel column chromatography (with a gradual increase of MeOH from 0.5 to 1% in CH_2Cl_2) to give iboga scaffold **6a** (34 mg, 31%) as a light brown solid. R_F = 0.52 (CH_2Cl_2/MeOH, 16:1); mp 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (br s, 1H), 7.47 (dd, J = 6.3, 2.1 Hz, 1H), 7.26 (dd, J = 6.6, 2.4 Hz, 1H), 7.14–7.09 (m, 2H), 3.73 (s, 3H), 3.58 (t, J = 2.1 Hz, 1H), 3.39–3.26 (m, 2H), 3.21–3.15 (dd, J = 14.5, 4 Hz, 1H), 3.02–3.11 (m, 3H), 2.76–2.71 (ddd, J = 10.93, 5.4, 2.2 Hz, 1H, H-16), 2.70–2.62 (m, 1H), 2.40–2.33 (dm, J = 12 Hz, 1H), 2.08 (m, 1H), 1.98 (m, 1H), 1.79–1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 141.0, 134.7, 129.8, 121.2, 119.3, 118.0, 110.3, 109.6, 56.9, 54.0, 52.0, 49.3, 45.9, 39.8, 34.4, 26.0, 25.9, 20.4; IR (KBr): ν 3398, 3055, 2926, 2866, 1732, 1614, 1460 cm^{-1}; HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{22}N_2O_2H^+$ 311.1754; found 311.1753.